Contents

Editorial

Surveillance of Indians with liver cirrhosis for treatable hepatocellular carcinoma: another enigma  K M Mohandas 261

Original Articles

Risk factors for esophageal cancer in Serbia  Zorana Gledovic, Anita Grgurevic, Tatjana Pekmezovic, Slobodan Pantelic, Darija Kisić 265

Time to recognize atypical celiac disease in Indian children  Abhinav Sharma, Ujjal Poddar, Surender Kumar Yachha 269

Incidence of hepatocellular carcinoma among Indian patients of cirrhosis of liver: an experience from a tertiary care centre in northern India  Shashi Bala Paul, Vishnubhatla Sreenivas, Manpreet Singh Gulati, Kaushal Madan, Arun Kumar Gupta, Sima Mukhopadhyay, Subrat Kumar Panda, Subrat Kumar Acharya 274

Clinicopathological predictors to predict sustained viral response rates in patients with chronic hepatitis C infection  J agdish S Nachnani, Raja Gidwani, Esmat Sadaddin, Wendell K Clarkston, Rusell Fiorella, Laura M Alba 279

Short Report

Portal venous thrombosis after umbilical vein catheterization  Seddigheh Hosseinpour Sakha, Mandana Rafeey, Mohammad Khazem Tarzamani 283

Review

Epidemiology of inflammatory bowel disease in Asia  Ajit Sood, Vandana Midha 285

Case Report

Extensive gastrointestinal tract and thyroid involvement with Wegener's granulomatosis  Raja Shekhar Reddy, Sappati Biyyani, Privi Pauskar, Nabil M Fahmy, James F King 290

Case Snippets

Acral and palmo-plantar hyperpigmentation in a patient with disseminated hepatocellular carcinoma  Rohit Goyal, Sreenivasa Baba Chalamalasetty, Kaushal Madan, Shashi Bala Paul, Raman Arora, Rajni Safaya, Subrat K Acharya 292

Primary intestinal lymphangiectasia as a component of autoimmune polyglandular syndrome type I: a report of 2 cases  Govind K Makharia, Nikhil Tandon, Neil de Jesus Rangel Stephen, Siddhartha Datta Gupta, Rakesh K Tandon 293

Letters

Iron deficiency anemia in Asians and Caucasians -- Any differences?  Pierre Ellul 296

HBeAg negative chronic hepatitis B with persistently normal serum transaminase and low HBV DNA can cause significant liver disease  Mamun-Al-Mahtab, Salimur Rahman, Mobin Khan, Md. Kamal, Ayub Al Mamun 297

Screening for hepatocellular carcinoma in hepatitis B and C chronic carriers in Iran  A Fani, I Fani, B Eshratie, P Samadian, P Fani, Y Gorishi 297

Stomach cancer incidence among males in Golestan province, Iran  Abdoljalal Marjani, Mohammad J avad Kabir, Shahriyar Sænnani 299

Octreotide in congenital chylous ascites an avoid requirement of total parenteral nutrition  Rakesh Mishra, Sanjeev Kumar 299

contd. on page iii ...

For online submission of articles and viewing full text of publications, visit the Journal website at www.indianjgastro.com

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Contents (contd.)

Mantle cell lymphoma (multiple lymphomatous polyposis) of gastrointestinal tract
M Murugesh, Veerendra Sandur, Niraj Sawalake, Madhu Sasidharan, Sanjay Altekar, Umang U Rathi, Mukta R Ramadwar, Pravin M Rathi 300

Transient neurotoxicity due to 5-fluorouracil
B Selvamani, Reena George, J Subhashini 301

Portal hypertension associated with sickle cell disease. Is there a coexistent liver disease?
Saju Xavier 302

Images

Mediastinal masquerade S Sankar, M Subramanian, K R Balakrishnan, Richard Saldanha 303
Detection of gall bladder cancer metastases in rare sites by PET scan Parul J Shukla, Savio G Barreto, Shailesh V Shrikhande, Mohandas KM, Purandare N, Rangarajan V 303

Gastroenterology Elsewhere 305
India Elsewhere 306

Announcements

Indian Journal of Gastroenterology J Mitra Memorial Award 268
Acknowledgment 295
News and Notices 304
Index to Advertisers 278
Instructions to Contributors 307
Background/Aim: Despite bearing the main burden of HCC, prospective studies from developing countries are lacking. This prospective observational study was designed to estimate the incidence of HCC among Indian patients with hepatic cirrhosis.

Methods: Between April 2001 and November 2004, we enrolled 301 patients with liver cirrhosis. Patients found to be free of HCC using baseline abdominal ultrasound, triple-phase computed tomography (TPCT) and serum alpha-fetoprotein (AFP) levels were followed up prospectively for detection of HCC using ultrasound and AFP every 6 months, and TPCT annually. Results: Among the 194 patients (mean age [SD] 45.1 [±13.1] years; male:female 6.1:1.0) followed up, 154 had Child’s A and 40 had Child’s B disease. The causes of cirrhosis were: hepatitis B-71 (36.6%), hepatitis C-54 (27.8%), dual infection with hepatitis B and C-12 (6.2%) and others including autoimmune, alcoholic and cryptogenic cirrhosis 57 (29.4%). During a cumulative follow up period of 563.4 person-years, 9 cases of HCC were detected, with an incidence rate of 1.60 per 100 person-years.

Conclusion: In our study, the incidence of HCC among patients with liver cirrhosis was intermediate, being lower than that in Japan but higher than that reported from Europe. [Indian J Gastroenterol 2007;26:274-278]
were quantitated using an in-house competitive PCR (CT-PCR) described earlier. The sensitivity of qualitative PCR for HBV DNA was 100 copies/mL and HCV RNA 500 copies/mL, and the same for CT-PCR was 10^2 copies/mL. These tests were done at initial presentation and every three months thereafter in patients treated with antiviral drugs. Serum alpha-fetoprotein (AFP) was estimated using a particle enzyme immunoassay (Axsym System; Abbott Laboratories, Abbot Park, Illinois, USA; normal range <20 ng/mL).

**Radiological investigations**

Abdominal ultrasonogram (US) and triple-phase CT (TPCT) were done at the time of enrolment. US was performed using a Philips HDI 5000 unit by two experienced investigators. Color and power Doppler were used for evaluation of the vessels and any mass lesion detected on US. Features of chronic liver disease and characteristics of any mass lesion in liver were noted. In case of disagreement, a re-evaluation was done jointly and consensus arrived at. The sonologists were blinded to the findings of TPCT.

TPCT of the liver was performed on a sub-second helical CT scanner (Somatom Plus 4, Siemens, Erlangen, Germany). The liver was imaged without any contrast and after intravenous contrast in three (arterial, venous and delayed) phases. TPCT was interpreted independently by two investigators who were unaware of the US findings. If one of the radiological investigations showed a mass lesion, the US and TPCT were interpreted together along with serum AFP levels to arrive at a final diagnosis regarding the presence or absence of HCC, as described below.

MRI was performed in those selected cases in whom the diagnosis remained uncertain even after US and TPCT. Gradient recoil (GRE) fat-suppressed T1-weighted, turbo spin echo T2-weighted, in phase, out of phase and multiphasic post-gadolinium sequences were done.

**Follow up**

Patients found to be free of HCC at enrollment were followed up prospectively for the occurrence of HCC using US and AFP measurement every six months, and TPCT annually. Regular follow-up was ensured through phone calls, letters and scheduled appointments for the tests. The follow up period was estimated from the date of diagnosis or cirrhosis to either end of study (November 2004), death, or development of HCC. Follow up duration was expressed in person-years and incidence rate as events per 100 person-years.

**Sample size**

Sample size of the follow-up cohort was calculated so that incidence of HCC could be measured with a precision of 15% (α=0.15) at a confidence level of 95%. This yielded a sample size of 170 subjects. Addition of 10% dropouts and loss to follow up led to a final sample size of 187.

**Definitions**

Diagnosis of cirrhosis was made on the basis of clinical, biochemical and endoscopy findings. Liver biopsy was done whenever considered necessary. Patients were classified as freshly-diagnosed cirrhosis if the duration of cirrhosis was less than 3 months at enrollment in the study; the rest were classified as having previously-diagnosed cirrhosis.

HBV cirrhosis was diagnosed when detectable HBsAg in serum was present. HCV cirrhosis was diagnosed with detectable anti-HCV and/or HCV RNA or both in serum. Replicating HBV infection was considered when these patients of cirrhosis had detectable HBeAg and/or HBV DNA in sera. Replicating HCV infection was diagnosed with detectable HCV RNA in the sera.

Diagnostic criteria followed for HCC were the modified European Association for Study of Liver (EASL) criteria. These consisted of a) either fine needle aspiration cytology (FNAC) or b) any two of the following three criteria: AFP level >300 ng/mL, arterIALIZATION of the mass on TPCT, arterIALIZATION of mass on MRI. The latter was performed infrequently, only in patients who had arterial enhancement at TPCT with normal serum AFP levels and equivocal FNAC. HCC was staged according to the Barcelona Clinic Liver Cancer (BCLC) Staging.

**Results**

Three hundred and one patients with liver cirrhosis were screened for HCC during the study period. Of these, 107 were found to have HCC. The remaining 194 patients who were free of HCC at enrollment constituted the follow-up cohort. Of these 194 patients, 154 belonged to Child class A and 40 to class B. The mean (SD) age of these patients was 45.1 (13.1) years with a male-female ratio of 6.1:1. Ninety-six patients were newly diagnosed cases whereas 98 had previously diagnosed cirrhosis.

The distribution of etiology was: HBV 71 (36.6%), HCV 54 (27.8%), dual infection with HBV and HCV 12 (6.2%), and other causes 57 (29.4%; includes autoimmune, alcoholic or cryptogenic cirrhosis). Vi-
Incidence of HCC in cirrhosis

Paul, Sreenivas, Gulati, Madan, Gupta, Mukhopadhyay, et al

Incidence of HCC in cirrhosis was observed in 59/83 (71%) patients with HBV infection and 38/66 (58%) patients with HCV infection. Mean AFP level of the cohort at enrolment was 17.5 (45.7) ng/mL (median 5.1; interquartile range 2.9-9.6). At the time of enrolment, 85% of the patients had AFP level below 20 ng/mL, whereas 1% had a level >300 ng/mL.

These 194 patients were followed up during the study period by US and AFP every 6 (±1.6) months and TPCT scan every 12 (±2) months. A cumulative follow up of 563.4 person-years (mean 34.9 months, median 25.5 months) was accomplished. Nine patients (age range 43 - 71 years, all men) developed HCC on follow up. The incidence of HCC among patients with liver cirrhosis was 1.60 (95% CI 0.55-2.64) per 100 person-years (Table 1). The incidence of HCC among the newly diagnosed cases of cirrhosis was 3.53 per 100 person years (95% CI 0.07 – 6.99). All the remaining patients of cirrhosis in the cohort continued to be free of HCC till the end of the study or death.

Four of nine patients who developed HCC were newly diagnosed cases of cirrhosis (median [range] duration 16 [9-26] months), while five were known cirrhotics for a variable duration (66 [44-152] months). Four patients had HBV and HCV infection each and one had dual infection with HBV and HCV. All these patients had replicating HBV/HCV infection and were in Child A cirrhosis at the time of detection of HCC. Incidence of HCC was similar among patients with HBV and HCV infection (Table 2). These 9 HCC cases picked up on surveillance had a baseline AFP level ranging from 2.5-40.1 ng/mL. At the time of detection of HCC, the AFP level of only one case was >300 ng/mL while the remaining 8 HCC cases had levels of 4.1, 5.4, 7.0, 10.3, 11.8, 13, 102 and 135 ng/mL, respectively.

Six patients (single lesion 4, multiple 2) had small sized (<5 cm diameter) HCCs, detected at 11, 13, 22, 29, 36 and 37 months after enrollment, respectively. Three patients (single 1, multiple 2) had large (>5 cm) HCCs, detected at 6, 8 and 13 months after enrollment, respectively. Three patients in whom the HCC was detected at a period less than a year, the tumors were picked up on US. They subsequently underwent TPCT. These patients were definitely free of HCC at US and TPCT at the time of enrollment. In the remaining 6 patients, HCC was detected both on US and TPCT. MRI was done in two of nine cases of HCC picked up on surveillance. The final diagnosis in these 9 cases was made on imaging (n=2), imaging plus cytology (n=6) and on imaging, AFP and cytology (n=1).

Of these 9 HCC patients, 4 were found to be at BCLC-A stage and survived for 9, 11, 43 and 52 months, respectively. Two patients were at BCLC-B stage and survived for 58 months each (with treatment), while the other died at 2 months without treatment. The remaining 3 patients were at BCLC-C stage and only one could be offered palliative therapy and survived for 7 months while the other two died at 4 and 5 months each as no definite therapy could be offered to them.

Discussion

In India, the mean incidence of HCC (per 100,000 population) in the four population-based cancer registries in the nineties was 2.77 for males and 1.28 for females. HCC accounted for 1.9% of the 24,975 cases of cancers recorded at 6 registries put together; the proportion ranging from 1.1% (94/8763) in Delhi to 5.3% (10/187) in Barshi rural registry. How-

<table>
<thead>
<tr>
<th>Patients</th>
<th>Number</th>
<th>Follow up Cumulative (years)</th>
<th>Mean (months)</th>
<th>Median (Range) (months)</th>
<th>Developed HCC (n)</th>
<th>Incidence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed</td>
<td>96</td>
<td>113.33</td>
<td>14.2</td>
<td>9.5 (0 - 44)</td>
<td>4</td>
<td>3.53 ( 0.07 - 6.99)</td>
</tr>
<tr>
<td>Previously diagnosed</td>
<td>98</td>
<td>450.09</td>
<td>55.1</td>
<td>46 (4 -181)</td>
<td>5</td>
<td>1.11 (0.14 - 2.08)</td>
</tr>
<tr>
<td>Total</td>
<td>194</td>
<td>563.4</td>
<td>34.9</td>
<td>25.5 (0-181)</td>
<td>9</td>
<td>1.60 (0.55 - 2.64)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Etiology of cirrhosis</th>
<th>Number</th>
<th>Follow up Cumulative (years)</th>
<th>Mean (months)</th>
<th>Median (Range) (months)</th>
<th>Developed HCC (n)</th>
<th>Incidence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>71</td>
<td>166.25</td>
<td>28.1</td>
<td>24</td>
<td>4</td>
<td>2.41 (0.05 - 4.76)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>54</td>
<td>168.83</td>
<td>36.4</td>
<td>23</td>
<td>4</td>
<td>2.44 (0.05 - 4.83)</td>
</tr>
<tr>
<td>HBV + HCV</td>
<td>12</td>
<td>29.83</td>
<td>34.9</td>
<td>25.5</td>
<td>1</td>
<td>3.35 (0.0 - 9.92)</td>
</tr>
<tr>
<td>Others</td>
<td>57</td>
<td>203.50</td>
<td>42.8</td>
<td>32</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
ever, the incidence of HCC in patients of cirrhosis has not been estimated in India earlier.

In the present study, the incidence rate has been estimated to be 1.60 per 100 person-years. The incidence in the newly diagnosed patients of cirrhosis was 3.53 per 100 person-years. The lower incidence in the previously diagnosed patients (1.1 per 100 person years) indicates possibly a survival bias, as they represent the ‘survivors’ of the ‘original cohort’ whose counterparts may have developed HCC and died.

In the 9 HCC patients detected on surveillance, 3 patients were diagnosed to have HCC at less than a year (6, 8 and 11 months). All these cases like others had undergone baseline US, AFP and TPCT at enrollment and were free of HCC at that stage. However, imaging techniques have a known fallacy of having very low sensitivity for tumors <1 cm.1 But for all practical purposes, the cohort was free of HCC at enrollment; therefore tumors detected at these periods of follow up should be viewed as detection on surveillance.

In various studies on HCC surveillance among patients of cirrhosis from different countries, the reported annual incidence ranged from 1.0% to 5.8% per year.14,15 Thus, the incidence of HCC in India is somewhat lower than European and other Asian countries. Studies among immigrant populations in Singapore and Australia, also indicate that Indians, in comparison to Malay and Chinese populations, are less prone to HCC.16

Risk of HCC is higher in patients of cirrhosis caused by viral infections compared to non-viral causes.14 In different Indian studies, almost half of HCC patients have underlying HBV infection; while over a quarter have HCV infection.15 The attributable fractions of HCC for HBV and HCV infections in Japan and Europe / US are 20%-22% and 60%-63%, respectively.17 In recent years, an improved understanding of viral genotypes has helped in explaining differential progression of HBV and HCV infections to HCC in different populations. Genotypes of HBV (A and D) and HCV (2, 3, 5 and 6) predominantly prevalent in India are less virulent and are associated with less frequent progression to HCC than other genotypes.18,19 This may be a critical additional reason for a relatively low risk of HCC among Indian patients of liver cirrhosis. Additionally, host characteristics might also be responsible for lower incidence of HCC among Indian patients of cirrhosis.

We found an equal proportion of cases of HBV and HCV cirrhosis developing HCC. Persistent HBV and HCV infections are the most important causes of HCC worldwide and have a variable geographical distribution. Various Indian studies have reported HBV infection as the predominant risk factor of HCC.20,21 Hepatitis B surface antigen (HBsAg) positivity in Indian HCC patients varies from 36% to 74%, with an average of 47%.13 It is estimated that nearly 42.5 million people in India are HBsAg positive.22 The prevalence of anti HCV antibody in the Indian population varies from 0.3% to 1.8%.23,24,25 In India, HBV transmission is a combination of mainly horizontal (75%) and vertical modes (25%), occurring mostly in childhood.26 HCV is an adult disease acquired mainly through the parenteral route.19,25

In conclusion, the present prospective cohort study reveals the HCC incidence among Indian patients of cirrhosis as 1.6% per year. Using this estimate of the incidence of HCC, the cost effectiveness of the surveillance program employing six monthly US and AFP with annual TPCT has also been estimated.26 This cost per HCC case detected is exorbitant for low / middle income countries like India.

Our study has some limitations. Due to small number of HCC cases detected, the risk factors of HCC could not be ascertained. Secondly, this being a hospital-based study, a referral bias leading to high prevalence of HCC in cirrhosis was unavoidable. However, it may be noted that on account of a very large population (approximately 1 billion), the number of HCC patients in India would still be enormous, despite the low incidence.

References
4. In India, HBV transmission is a combination of mainly horizontal (75%) and vertical modes (25%), occurring mostly in childhood.26 HCV is an adult disease acquired mainly through the parenteral route.19,25
5. In conclusion, the present prospective cohort study reveals the HCC incidence among Indian patients of cirrhosis as 1.6% per year. Using this estimate of the incidence of HCC, the cost effectiveness of the surveillance program employing six monthly US and AFP with annual TPCT has also been estimated.26 This cost per HCC case detected is exorbitant for low / middle income countries like India.

Incidence of HCC in cirrhosis

74.


